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FOREWORD

This report was prepared in the Radiobiology Branch of the USAF School of Aerospace Medicine and the Radiobiological Laboratory of the University of Texas, Austin, Tex., under contract No. AF 41(609)-2005 and task No. 775702. The paper was submitted for publication on 18 March 1966.

This experiment was the second of a series of studies designed to examine the effects of low levels of mixed ionizing radiations on the primate. The study was initiated in 1954 by personnel then assigned to the School of Aviation Medicine and the Radiobiological Laboratory. These workers designed the experimental protocol and conducted the exposures under the direction of Colonel Pickering. The animals were maintained and studied at the Radiobiological Laboratory from January 1954 to May 1964. This report, therefore, summarizes the work of several investigators over a period of years. The authors wish to acknowledge the help of personnel in the following branches of the School: Radiobiology, Ophthalmology, Biometrics, and the Veterinary Sciences Division—especially the contributions of D. R. Anderson, J. Auxier, R. E. Benson, D. V. L. Brown, T. Burns, J. F. Culver, R. T. Davis, E. F. Galloway, J. J. Ghidoni, G. S. Hurst, S. P. Kent, G. M. Krise, L. Logie, L. McClurkan, J. G. McKinley, R. C. McNee, J. A. Overall, J. A. Pitcock, R. M. Ritter, E. M. Robinson, S. C. Sigoloff, G. Thoma, G. R. Vela, F. S. Vogel, N. Wald, C. M. Williams, D. B. Williams, S. Wilson, and R. J. Young.

The experiments reported herein were conducted according to the "Principles of Laboratory Animal Care" established by the National Society for Medical Research.

This report has been reviewed and is approved.

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ABSTRACT

The radiobiologist has been concerned with both the early and late effects of ionizing radiations administered in small increments over a relatively long period of time. In 1954, 48 *Macaca mulatta* primates were exposed to an irradiation schedule involving fast neutrons and gamma rays which resulted in the accumulation of doses from 77 to 614 rep. Since the exposure schedules afforded rest and recovery periods, it was proposed and found that the effects were less severe than the effects from comparable doses given acutely.

The principal early effect noted was a transient decrease in peripheral cell counts for leukocytes and erythrocytes noted in the higher dose group. The principal late effects involved a reduction in visual acuity in the 307- and 614-rep groups; a series of definitive, continuing behavioral changes; and evidence of dose-dependent testicular damage as noted by histopathologic methods. Evaluation of the data suggests that radiation was probably not a factor in life-shortening.

SOME EFFECTS OF MIXED IONIZING RADIATIONS ON RHESUS PRIMATES EXPOSED UNDER LABORATORY CONDITIONS

I. INTRODUCTION

Faced with the responsibility of supplying information on the effects of chronic exposure to low levels of high energy radiation upon USAF personnel, the School of Aerospace Medicine in 1954 began studies designed to reveal the effects of such radiations on the rhesus primate. The experiment reported herein was concerned with the exposure of primates to graded mixtures of gamma rays and neutrons from chemical radiation sources.

This program was a logical continuation of studies conducted at the Oak Ridge National Laboratory where a shielded high-level reactor source was employed. The objectives were to furnish scientific information that would be useful in dealing with the biomedical problems which were anticipated from the use of nuclear-propelled aerospace vehicles and which have been defined by Pickering et al. (29). A low-level mixed radiation laboratory was constructed, designed specifically to meet the needs of the nuclear-propulsion program, but it also contained inherent flexibility to make it useful in other experiments of interest to the School of Aerospace Medicine. The "Mixed Irradiation Facility" was used for the irradiations to be described.

The *Macaca mulatta* was chosen, and the methodology employed was based on classic medical, physiologic, and psychologic technics. The experimental avenues of investigation were not limited. The investigators placed great emphasis on the reaction of formed peripheral blood elements, visual phenomena, life span, and behavioral characteristics to chronic fractionated exposure to ionizing radiations.

II. SUMMARY

The following research areas have been studied herein: (1) hematology, (2) behavior and performance, (3) testicular histopathology, (4) cataractogenesis, (5) clinical chemistry, (6) longevity, (7) clinical symptomatology, and (8) pathology. In the first three areas listed above, the following radiation effects were found: a transient and relatively early decrease in white blood cells and red blood cells, a more definitive and long-lasting effect on behavioral measures, and a dose-dependent observation of histologic sterility in the tubules of the testes. No evidence was found that radiation invoked cataractogenesis or altered the clinical chemistries measured. There was no evidence that irradiation was a primary contributor to any of the other changes or findings noted by either the clinician or pathologist.

III. METHODS

Animals

Forty-eight male *Macaca mulatta* were imported from India. They ranged in age from 27 to 39 months (based on dentition) and in weight from 4 to 9 pounds (1, 33, 34). The care and feeding of these animals have been described by Young et al. (34); these conditions were maintained throughout the post-irradiation confinement with only minor variations.

Irradiation

All experimental animals were exposed to radiation in a specially constructed chamber, fitted with an overhead crane, which permitted

the simultaneous exposure of 6 animals in individual cages. The radiation flux was controlled by varying the source-to-animal distance, while total dosage was determined by time of exposure. All exposures were for a period of 16 hours and were repeated at intervals of 4 or 12 days until the desired cumulative dose was achieved. The schedule and doses are shown in tables I and II.

TABLE I

Irradiation schedule (1954)

Date	Group	Date	Group	Date	Group
Apr.		21	C	July	
11	AB	22	EF	1	EF
12	EF	23	G	2	G
13	G	24	H	3	H
14	H	25	D	4	AB
15	C	26	EF	5	EF
16	EF	27	G	6	G
17	G	28	H	7	H
18	H	29	AB	8	C
19	D	30	EF	9	EF
20	EF	31	G	10	G
21	G			11	H
22	H	June		12	D
23	AB	1	H	13	EF
24	EF	2	C	14	G
25	G	3	EF	15	H
26	H	4	G	16	AB
27	C	5	H	17	EF
28	EF	6	D	18	G
29	G	7	EF	19	H
30	H	8	G	20	C
		9	H	21	EF
May		10	AB	22	G
1	D	11	EF	23	H
2	EF	12	G	24	D
3	G	13	H	25	EF
4	H	14	C	26	G
5	AB	15	EF	27	H
6	EF	16	G	28	AB
7	G	17	H	29	EF
8	H	18	D	30	G
9	C	19	EF	31	H
10	EF	20	G		
11	G	21	H	Aug.	
12	H	22	AB	1	D
13	D	23	EF	2	EF
14	EF	24	G	3	G
15	G	25	H	4	H
16	H	26	C	5	D
17	AB	27	EF	6	EF
18	EF	28	G	7	G
19	G	29	H	8	H
20	H	30	D	9	AB

TABLE I (contd.)

Date	Group	Date	Group	Date	Group
10	EF	Sept.		Oct.	
11	G	1	H	4	D
12	H	2	AB	8	AB
13	C	3	EF	12	C
14	EF	4	G	16	D
15	G	5	H	20	AB
16	H	6	C	24	C
17	D	7	EF	28	D
18	EF	8	G		
19	G	9	H		
20	H	10	D	Nov.	
21	AB	11	EF	1	AB
22	EF	12	C	5	C
23	G	13	H	9	D
24	H	14	AB	13	AB
25	C	15	EF	17	C
26	EF	16	G	21	D
27	G	17	H	25	AB
28	H	18	C	29	C
29	D	22	D		
30	EF	26	AB		
31	G	30	C	Dec.	
				4	D

Cobalt-60 and a mixture of polonium and beryllium were employed as the sources of gamma rays and fast neutrons, respectively. The size of the radiation field, the proportion of gamma rays to neutrons, and the total flux were determined by the number and position of radioactive sources inserted into the chamber. Figures 1 and 2 give plans and dimensions of the structure, position of radiation sources, and position of the animals.

Dosimetry

Prior to the irradiation of animals, the radiation field was calibrated by comparison to National Bureau of Standards gamma ray sources and by Mounds Laboratory PoBe neutron sources. Gamma rays were measured by the Lauristsen electroscope, the Victoreen electroscope, and photographic films, while neutron sources were measured by the Hurst proportional counter, a pulse integrating system, and a nuclear emulsion technic. The measurements obtained with phantoms and, subsequently, with irradiated animals carrying dosimeters indicated that variation in the radiation field was less than 6%.

TABLE II

Dose and dose rate schedules of mixed radiation

Group	Number of animals	Number of exposures	Gamma dose rate (mr/hr.)	Total gamma dose (r)	Neutron dose rate (mrep/hr.)	Total neutron dose (rep)
A	6	20	0	0	0	0
E	6	40	0	0	0	0
B	6	20	218	70	22	7
F	6	40	218	140	22	14
C	6	20	436	140	44	14
G	6	40	436	284	44	28
D	6	20	872	280	87	28
H	6	40	872	557	87	56

Exposures were at 4-day intervals and lasted for a period of 16 hours for groups F, G, and H, while groups B, C, and D were exposed for 16 hours at 12-day intervals.

Evaluation of results

The data obtained from these animals have been studied by statistical methods where these were deemed to be appropriate. The hematology data were analyzed by the Biometrics Department of the School of Aerospace Medicine and included peripheral blood values for white blood cells, red blood cells, lymphocytes, segmented cells, eosinophils, reticulocytes, platelets, hemoglobin, and hematocrit (24). The significance of observed differences was determined by analyses of variance for repeated measures. The behavioral and performance scores were analyzed by the various investigators themselves by use of both parametric and nonparametric statistics.

Hematology

Measurements of the circulating blood constituents of the animals were performed at intervals throughout the experiment. Blood samples were obtained weekly for 3 months before exposure to radiation and during the irradiation term. For the subsequent 3 months, measurements were performed monthly; thereafter, every 6 weeks. From 1957 through 1963, hematologic measurements were obtained less frequently, but no less than three samplings were obtained in any one year. The methods employed were based on classic hematologic technics previously described by Krise and Wald (12) and by Melville et al. (25). Starting in 1962, erythrocyte and leukocyte counts were made with the Coulter automatic cell counter.

Blood chemistry

The blood serum levels of glutamic oxalacetic and glutamic pyruvic transaminase enzymes were measured in September of 1961 in those animals still alive. A colorimetric reaction described by Frankel and amended by the Sigma Chemical Company (31) was used. Duplicate measurements were obtained on each sample submitted. In November and December of 1963 the serum transaminase levels were measured again on 4 animals by use of methods described by Warner-Chilcott (32, 33).

Ten milliliters of blood were drawn from certain animals on 15 May 1956, 1 June 1956 15 June 1956, and 10 January 1957, and submitted to the 4th Army Area Medical Laboratory for clinical analyses. Blood urea nitrogen, carbon dioxide level, calcium, sodium, potassium, and phosphorus were measured by standard laboratory methodology.

In November and December of 1963, blood from the surviving animals was analyzed for urea nitrogen, protein, and its ratio of albumin to globulin by the monoxime diacetyl reaction, the biuret reaction, and paper electrophoresis

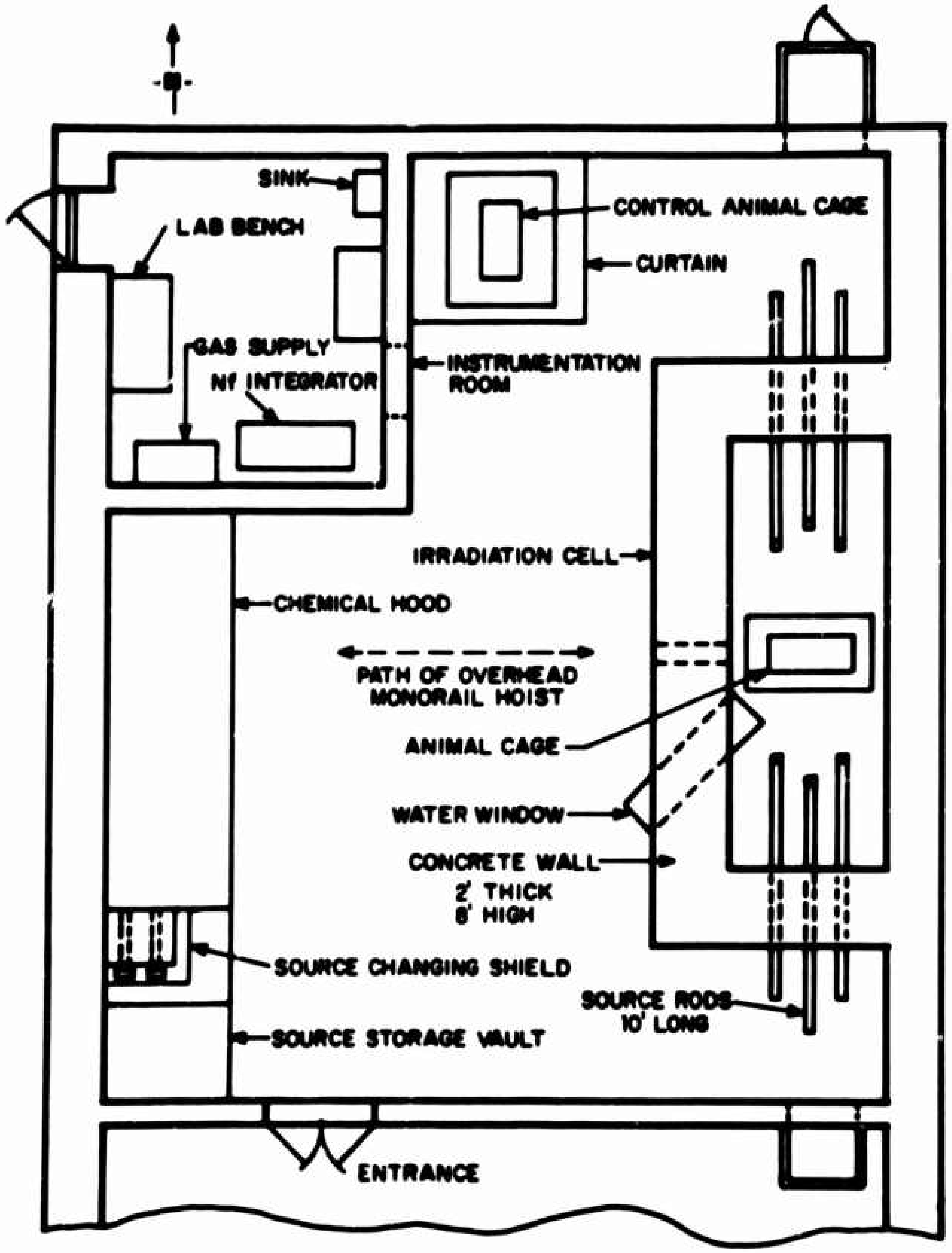

FIGURE 1

Floor plan of mixed radiation chamber.

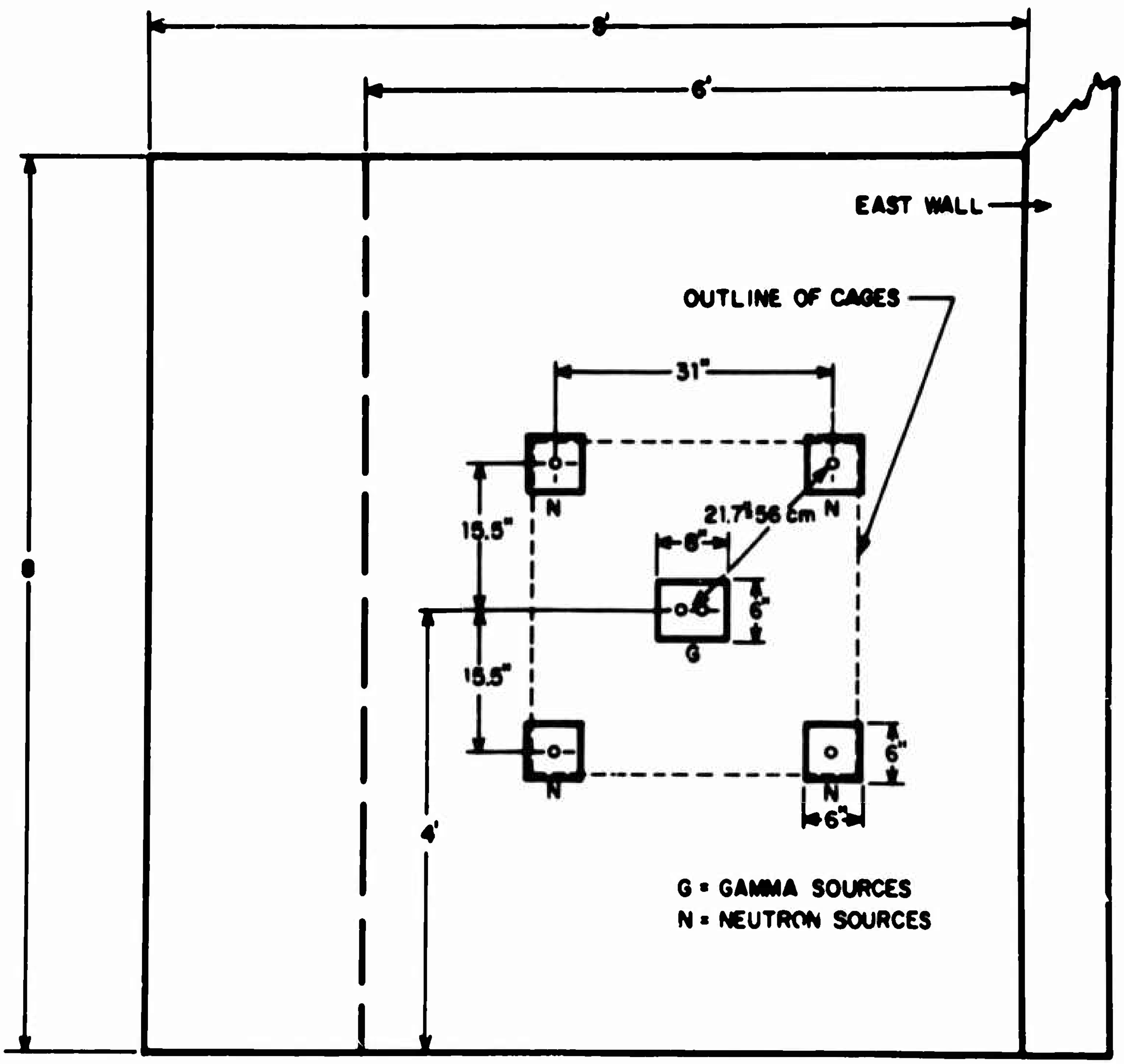

FIGURE 2

Diagram of arrangement of radiation sources in the south wall of the chamber.

separation, respectively. Additionally, 4-day urine samples were assayed for total amino acid, creatinine, and urinary sugars.

Ophthalmology

Examinations for abnormalities of the eye and lens were performed on these animals from 1953 to 1959. The animals were tranquilized with chlorpromazine and placed in restraining boxes. The pupils were then dilated with atropine and examined with a slit lamp in a darkened room (25, 34).

Clinical findings

The care of the animals included daily "health checks" and frequent examinations by trained animal handlers and veterinarians. Records of the condition and appearance of

each animal were posted and included in a permanent file. Periodic parasitologic and bacteriologic examinations were performed on each animal during its postirradiation survival period.

Life span and necropsy findings

Autopsies were performed on all animals that died. The autopsies consisted of descriptions of gross and microscopic findings, as well as a statement of the cause of death and of conditions contributing to the fact of death.

Behavioral studies

The diversity of studies presented precludes an exposition of the specific procedures involved. In consequence, the general procedures used in each test yielding positive results will accompany the presentation of such results; all specific procedures are available in the referenced publications.

Many of the studies have followed the precedent established by Davis et al. (9) and have treated each set of experimental results in terms of comparisons of subjects within untreated control, low-dose, and high-dose subgroups. Treatment groups A and E comprise the untreated control subgroup; the treatment groups B, C, and F, the low-dose subgroup; and treatment groups D, G, and H, the high-dose subgroup. In other words, many of the studies have dealt with a relative radiation dosage variable, rather than an absolute dosage variable.

IV. RESULTS

Hematology

Statistical analyses of the hematologic data obtained during the first 20 months of the experiment indicated that leukocyte levels were depressed in the animals exposed to radiation when these were compared to nonirradiated controls. Erythrocyte levels on the 4-day interval showed a tendency to depression: compare the medium-dose and high-dose groups with the controls (fig. 3). The reticulocyte levels, as expected, reflected the red blood cell responses. Figure 3 shows the nature of these radiation effects on the blood of irradiated primates. Statistical analyses of the other blood constituents indicated no detectable alterations. These data were compiled and analyzed by McNee and Ritter (24).

The data obtained from the 20th to the 50th month of the experiment were again analyzed by McNee and Ritter (24). Anderson (1) reported on these data and concluded by stating that "These analyses indicated that there were no apparent long-term effects due to the irradiation on any of the blood variables analyzed . . . ." Anderson also discussed the effects of an incident of vitamin D intoxication on the primate colony of which the animals in this experiment were a part. Inadvertently, from February to May of 1955, the animals were supplied a diet high in vitamin D. As a result, several of the experimental animals died and those remaining revealed transient abnormal hematologic profiles. The effects of hypervitaminosis D on hematograms, however, did not impeach the conclusions obvious to the data referring to the latent effects of radiation on the primates (tables III and IV).

Tables V and VI reaffirm that low doses of ionizing radiation administered periodically to the primate over a prolonged period of time do not affect its hematologic characteristics. There are, however, transient effects evident during the irradiation period and immediate postirradiation period.

Clinical chemistry

The levels of glutamic oxalacetic and glutamic pyruvic transaminase in the blood of irradiated *Macaca mulatta* were measured twice. Table VII shows the results obtained in 1961, while the results for 1963 are included in table VIII. The data of table VII were not separated into groups of animals exposed at different time intervals. These values indicate that chronic exposure to mixed radiation had no latent effect on the transaminases in the blood of this primate.

The data in table VIII are remarkable only in two respects: no conclusions can be drawn with regard to radiation effects, and secondly,

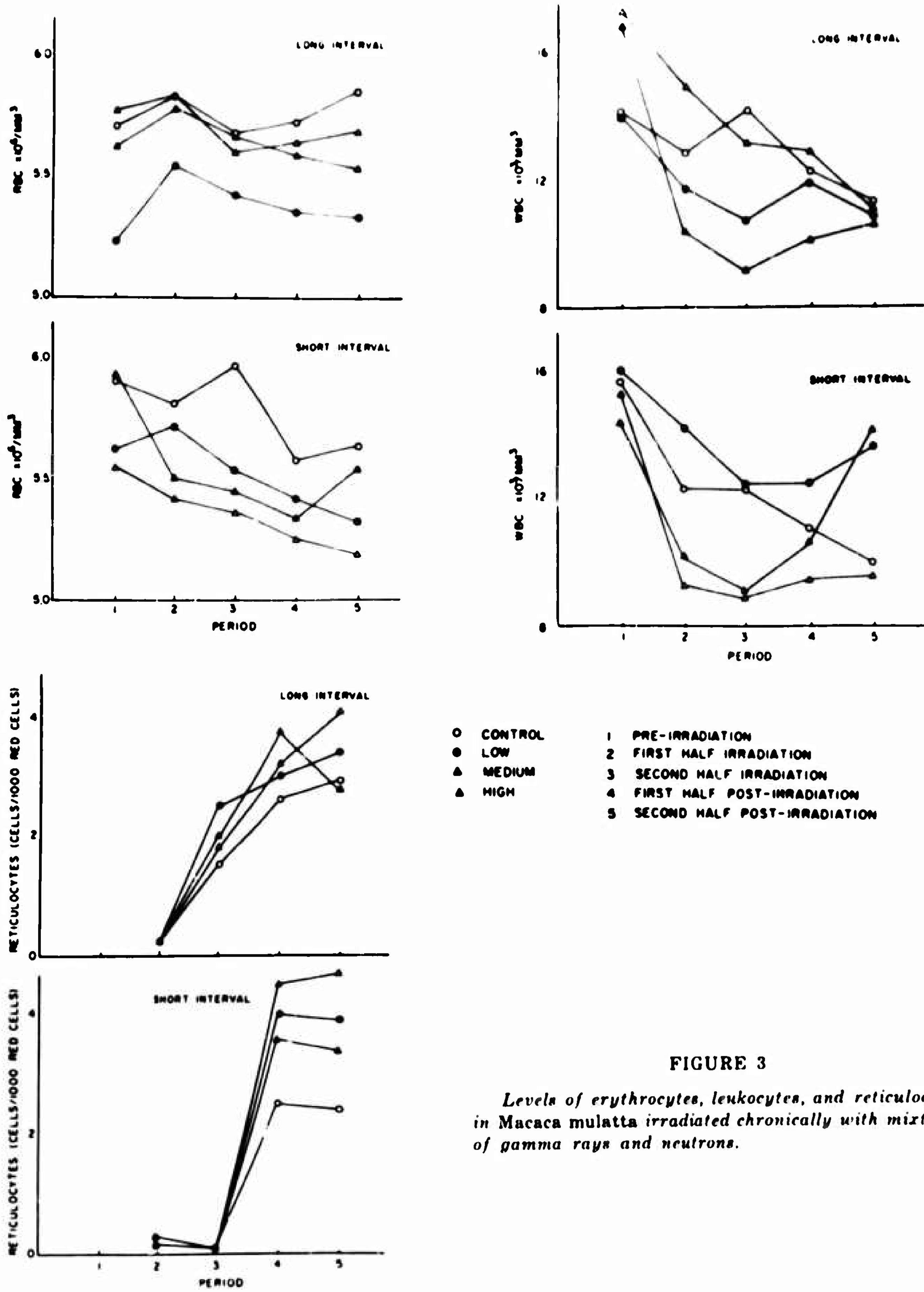

FIGURE 3

Levels of erythrocytes, leukocytes, and reticulocytes in Macaca mulatta *irradiated chronically with mixtures of gamma rays and neutrons.*

TABLE III

Mean values for hematologic measures during months 20 to 50 for the long interval

Group		Periods 1	2	3	4	5	6	7	8	9	10	11	12	13	14
								RBC × 10⁶/mm.³							
Control	(A)	5.57	6.15	6.32	6.33	6.23	6.10	6.10	5.64	5.68	6.36	6.46	6.35	6.04	6.19
Low	(B)	5.39	5.66	5.53	5.55	5.63	5.40	5.03	5.48	5.51	5.38	5.85	5.20	5.36	5.65
Medium	(C)	5.46	5.97	5.64	5.61	5.73	5.49	6.00	5.76	5.47	5.44	6.11	5.68	5.78	5.57
High	(D)	5.27	5.55	5.92	5.79	5.64	5.66	5.92	5.44	5.99	5.58	5.97	5.91	5.74	6.19
								WBC × 10³/mm.³							
Control	(A)	10.5	11.2	10.5	11.9	12.9	10.7	18.0	13.7	8.7	9.3	8.5	11.4	8.2	8.1
Low	(B)	11.8	11.1	8.6	12.2	9.2	9.8	12.7	14.5	7.7	8.2	7.5	7.5	7.6	7.9
Medium	(C)	11.2	12.8	10.3	9.9	9.4	12.5	13.2	11.8	9.7	8.2	7.8	11.3	8.8	8.3
High	(D)	10.8	9.7	9.8	10.6	12.0	9.4	17.5	10.1	9.6	9.1	10.2	10.0	7.9	8.4
								Platelets × 10³/mm.³							
Control	(A)	587.5	395.0	365.0	332.5	412.5	347.5	285.0	452.5	350.0	407.5	372.5	355.0	395.0	305.0
Low	(B)	536.0	376.0	406.0	394.0	462.0	378.0	414.0	432.0	332.0	410.0	438.0	348.0	338.0	364.0
Medium	(C)	536.7	423.3	500.0	373.3	503.3	470.0	420.0	503.3	406.7	450.0	413.3	363.3	436.7	286.7
High	(D)	514.0	382.0	498.0	448.0	516.0	436.0	354.0	430.0	438.0	482.0	484.0	446.0	464.0	436.0
								Lymphocytes (%)							
Control	(A)	66.5	74.5	63.8	53.3	55.8	52.8	40.0	33.0	56.8	49.5	55.3	45.3	42.0	46.8
Low	(B)	68.4	70.6	68.6	62.6	51.6	55.2	43.2	38.6	55.2	49.6	58.2	56.8	47.0	45.0
Medium	(C)	66.0	69.3	55.0	60.7	58.3	50.0	41.7	41.7	58.7	62.3	66.0	55.0	59.0	39.7
High	(D)	72.2	70.8	69.6	66.6	57.8	60.6	26.2	46.4	48.4	63.2	61.0	41.4	57.8	52.0
								Reticulocytes (%)							
Control	(A)	1.8	3.0	2.3	3.5	4.5	1.5	.5	4.3	2.5	1.8	5.8	2.8	3.0	
Low	(B)	2.2	1.6	2.0	3.2	3.8	1.0	.2	4.2	2.4	2.4	3.2	2.8	3.2	
Medium	(C)	1.0	3.3	2.0	4.0	3.7	2.0	.0	2.3	1.7	2.0	2.0	2.3	3.3	
High	(D)	2.2	1.8	2.6	4.6	4.2	3.0	.0	2.8	2.8	3.6	4.2	3.8	5.2	

the serum protein and serum transaminase values for animal No. 294+ mirror his clinical condition: wasted, debilitated, and partially paralyzed. The A/G ratio of 0.15 is attributable to both decreased albumin and increased beta and gamma globulin concentrations. The clinical condition of animal No. 294+ would not seem to be a primary function of either caging factors or radiation parameters.

Table IX shows the blood levels of various chemical constituents for *Macaca mulatta*. Differences between irradiated and control animals were not evident. All the values for these measurements were not within the normal levels reported for this animal (16). The high blood levels of urea nitrogen and of calcium ions found in the animals are attributable to hypervitaminosis D and not to radiation.

Ophthalmology

Originally, radiation-induced formation of cataracts of the lens was considered to be one of the most important exposure effects. The results reveal that, under these conditions, small doses of mixed radiation were not cataractogenic. Table X presents the ophthalmologic findings. The conclusions were extensively reviewed before this writing, and the authors are in agreement with Pickering et al. (29), who noted that the 48 animals

TABLE IV

Mean values for hematologic measures during months 20 to 50 for the short interval

Group		Periods 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
								RBC × 10^6/mm.^{3}								
Control	(E)	5.67	5.68	5.75	5.72	6.15	5.81	6.06	5.37	5.56	5.67	5.47	6.05	6.06	5.83	6.08
Low	(F)	5.30	5.16	5.45	5.51	5.84	5.45	5.54	5.12	5.27	5.37	5.69	5.34	5.88	5.86	5.66
Medium	(G)	4.99	5.15	5.27	5.30	5.66	5.62	5.30	5.33	4.90	5.69	5.55	5.39	5.72	5.50	5.39
High	(H)	5.43	5.25	5.62	5.97	5.54	5.35	5.58	5.22	5.43	5.65	5.61	5.86	6.38	6.08	5.80
								WBC × 10^3/mm.^{3}								
Control	(E)	11.1	11.2	11.5	10.9	11.3	12.8	14.7	14.7	9.7	8.1	10.5	8.7	12.3	9.8	8.7
Low	(F)	12.2	12.3	14.5	10.6	13.2	12.9	15.4	14.6	10.8	11.2	10.7	10.1	9.3	7.5	6.9
Medium	(G)	11.4	11.9	12.4	8.9	10.3	12.9	14.6	10.3	8.5	8.6	9.0	8.1	8.3	6.7	8.0
High	(H)	11.1	9.7	11.9	11.2	16.6	12.4	13.2	12.5	10.4	9.5	10.8	11.5	10.2	10.7	10.2
								Platelets × 10^3/mm.^{3}								
Control	(E)	458.3	386.7	535.0	401.7	496.7	335.0	443.3	493.3	435.0	361.7	436.7	438.3	451.7	421.7	350.0
Low	(F)	360.0	330.0	442.0	346.0	354.0	460.0	380.0	424.0	466.0	344.0	414.0	360.0	386.0	378.0	376.0
Medium	(G)	342.5	465.0	355.0	372.5	445.0	340.0	402.5	397.5	435.0	365.0	445.0	470.0	340.0	375.0	362.5
High	(H)	345.0	292.5	430.0	387.5	467.5	340.0	325.0	465.0	522.5	380.0	402.5	410.0	407.5	472.5	355.0
								Lymphocytes (%)								
Control	(E)	78.0	70.3	66.0	66.7	59.2	49.3	43.3	33.0	63.5	72.7	66.8	62.8	52.0	51.8	65.7
Low	(F)	79.4	70.2	69.8	80.0	60.6	50.4	46.2	34.2	61.4	77.2	63.2	69.8	66.6	62.6	50.8
Medium	(G)	76.8	65.3	73.8	75.8	50.0	54.0	25.8	37.5	57.3	70.0	67.5	65.0	41.3	58.5	49.8
High	(H)	82.0	81.0	75.3	62.8	56.3	55.5	41.3	37.8	60.3	76.8	64.3	65.0	57.3	60.8	65.8
								Reticulocytes (%)								
Control	(E)	2.5	1.8	4.3	.8	3.3	1.2	.3	.5	2.0	1.3	2.3	2.2	2.5	3.2	1.8
Low	(F)	3.4	1.4	6.0	1.2	3.4	1.6	.6	.2	3.4	1.2	2.2	6.2	3.4	3.2	3.0
Medium	(G)	8.0	5.0	5.8	2.3	1.8	3.5	.5	1.3	6.3	1.5	3.3	5.3	1.8	3.5	3.0
High	(H)	4.3	1.8	3.8	4.0	5.0	1.3	1.3	.3	2.0	1.5	1.0	4.8	2.8	2.5	2.8

TABLE V

Mean values for peripheral blood parameters long interval (12 days)—20 exposures

Number of animals*	Subgroup		Dose (rep)	RBC	Hb	HCT	WBC
			1959†				
4	Control	(A)	0	6.62	12.7	46.4	9.95
5	Low	(B)	77	5.85	11.5	42.8	8.92
3	Medium	(C)	154	6.17	12.1	43.3	10.02
4	High	(D)	308	6.16	12.0	44.5	8.32
			1960‡				
4	Control	(A)	0	5.70	12.0	45.2	9.79
4	Low	(B)	77	5.48	12.2	43.9	8.64
3	Medium	(C)	154	5.46	11.8	45.1	9.99
3	High	(D)	308	5.55	12.5	45.1	7.04
			1961§				
1	Control	(A)	0	5.53	11.7	42.0	9.62
3	Low	(B)	77	5.28	11.8	42.8	9.89
2	Medium	(C)	154	5.70	12.1	43.3	10.82
2	High	(D)	308	5.24	12.1	43.7	8.26
			1962‖				
1	Control	(A)	0	5.40	10.1	36.2	18.07
2	Low	(B)	77	4.98	11.8	39.1	9.58
1	Medium	(C)	154	6.30	14.0	46.3	10.84
1	High	(D)	308	5.74	12.8	43.7	11.13
			1963¶				
0	Control	(A)	0				
1	Low	(B)	77	5.24	11.9	39.0	8.63
0	Medium	(C)	154				
0	High	(D)	308				

*Note that the number of animals included in the mean is not always the same.

†Six samples taken during year on each surviving animal.

‡Eight samples taken during year on each surviving animal.

§Four samples taken during year on each surviving animal.

‖Three samples taken during year on each surviving animal.

¶Four samples taken during year on each animal except for one of group G which died during the interval between the January and May samplings.

exposed to mixed neutrons and gamma rays did not have radiation-induced cataracts for a 5-year period after exposure to radiation. A mild decrement in the visual acuity of animals receiving 308 and 614 rep of mixed radiation has been recorded (see "Behavioral Studies" under *Results*). Visual acuity was measured by the Landolt ring method. An eye examination ascertained that the visual impairment was not due to cataract or other anatomic lesions.

Life span and necropsy findings

The postirradiation survival of experimental animals was complicated by several factors extrinsic to the experiment: (1) high incidence of colitis-induced deaths in experimental animals, (2) incidence of deaths from other disease processes, and (3) effects of toxic doses of vitamin D in the food for a period of some 3 months during the early part of the experiment (11). Therefore, the effects

TABLE VI

Mean values for peripheral blood parameters short interval (4 days)—40 exposures

Number of animals*	Subgroup		Dose (rep)	RBC	Hb	HCT	WBC
			1959†				
4	Control	(E)	0	6.07	12.0	43.7	8.22
4	Low	(F)	154	6.31	12.1	44.2	8.31
4	Medium	(G)	308	6.06	11.9	43.6	8.32
4	High	(H)	614	6.24	12.4	44.9	8.31
			1960‡				
3	Control	(E)	0	5.38	11.8	43.2	7.36
3	Low	(F)	154	5.33	11.4	43.0	9.24
4	Medium	(G)	308	5.20	11.8	43.5	8.38
3	High	(H)	614	5.42	12.3	44.3	7.97
			1961§				
1	Control	(E)	0	4.84	11.4	40.4	6.09
2	Low	(F)	154	5.37	11.2	41.5	8.76
4	Medium	(G)	308	5.22	11.5	42.1	8.35
3	High	(H)	614	5.45	12.9	44.8	7.93
			1962‖				
1	Control	(E)	0	4.90	11.4	38.7	9.20
0	Low	(F)	154	—	—	—	—
2	Medium	(G)	308	5.13	12.6	41.3	8.47
2	High	(H)	614	5.52	12.7	41.9	8.58
			1963¶				
0	Control	(E)	0	—	—	—	—
0	Low	(F)	154	—	—	—	—
2(1)	Medium	(G)	308	5.02	12.2	39.7	7.95
2	High	(H)	614	5.82	12.4	41.2	11.9

*Note that the number of animals included in the mean is not always the same.

†Six samples taken during year on each surviving animal.

‡Eight samples taken during year on each surviving animal.

§Four samples taken during year on each surviving animal.

‖Three samples taken during year on each surviving animal.

¶Four samples taken during year on each animal except for one of group G which died during the interval between the January and May samplings.

of chronic exposure to these low levels of mixed radiation on the life span of *Macaca mulatta* cannot be inferred from this experiment, and the authors agree in this respect with Anderson (1) and with Pickering et al. (29). In figures 4, 6, and 7, the death patterns and times are noted.

Of the original 48 animals, 3 are now alive. Two died accidentally because of heater failure (197+, group G; 133+, group H), and 1 animal died during administration of anesthesia (298+, group D); 9 animals died during the vitamin D episode (145+, group A; 213+, group B; 366+, 55+, and 54+, group C; 361+, group D; 61+, group F; 143+, group G; 217+, group H); 1 was sacrificed (294+, group H); 1 died during the irradiation interval (306+, group A); and 1 was suspected of tuberculosis and was sacrificed in February 1963 (137+, group C). The diagnosis of tuberculosis was not confirmed at necropsy, although moderate calcification of the bronchi was noted.

TABLE VII

Levels (in Sigma-Frankel units) of serum glutamic-oxalacetic and glutamic-pyruvic transaminases in* Macaca mulatta *exposed chronically to mixed neutrons and gamma rays*

Animal No.	Total dose (gamma and neutrons—rep)	SGO-T	SGP-T	Average SGO-T	Average SGP-T
Group B					
103+	77	22-23	15-16	28	15
146+		30-29	15-15		
301+		32-32	14-14		
Group C					
101+	154	22-22	14-15	23	18
137+		24-24	23-21		
Group D					
60+	308	19-19	13-13	20	11
198+		22-21	8-8		
Group E					
304+	0	33-33	27-27	33	27
Group F					
37+	154	29-29	21-23	27	18
199+		24-24	14-15		
Group G					
40+	308	18-18	8-8	21	14
138+		22-21	18-18		
140+		27-28	13-13		
144+		17-17	15-15		
Group H					
52+	614	18-17	18-18	19	16
294+		19-19	15-15		
297+		19-19	17-16		

*One Sigma-Frankel unit of transaminase activity will form 1.82×10^4 μ of glutamate per minute at pH 7.5 and 25° C. (see ref. 31).

Deaths during the vitamin D episode occurred within a 4-month span (February—May 1956), and there were again no deaths for the next 31 months (until January 1959). From January 1959 to January 1964 deaths occurred as follows (excluding sacrifices, accidents, and transfer):

	'59	'60	'61	'62	'63	'64	Number alive
Controls	2	1	5	3	—	—	0
Irradiates	5	—	6	6	2	—	3
Total	7	1	11	9	2	—	3

Autopsy findings (fig. 4) showed that the majority of deaths were due to circumstances associated with the conditions of captivity.

Clinical observations

The clinical reports of the animals have been examined; on the group level, there are no changes which can be definitely attributed to irradiation. The clinical findings are summarized in figures 6 and 7.

The effect of chronic low levels of radiation on the testicular anatomy of the primates was investigated by Pitcock (30), who obtained

TABLE VIII

Clinical chemistries in late survivors (1963)

Determinations	No. 52+ Group H 614 rep		No. 294+ Group H 614 rep		No. 138+ Group G 308 rep		No. 103+ Group B 77 rep	
	Nov.	Dec.	Nov.	Dec.	Nov.	Dec.	Nov.	Dec.
SGO-T	15	14	11	22	17	14	10	17
SGP-T	4	7	2	8	5	8	4	5
BUN (mg. %)	22.5	17.5	22.5	20.0	20.0	20.0	27.5	25.0
Total protein (mg. %)	7.4	6.7	6.9	5.3	8.5	6.7	7.5	8.2
Albumin (mg. %)	3.9	3.5	1.7	0.82	4.2	3.2	4.0	4.5
Globulin (mg. %)	3.5	1.7	5.3	5.45	4.3	3.5	3.5	2.1
A/G ratio	1.13	1.03	0.32	0.15	0.96	0.93	1.13	1.13
α-Globulin	0.66	0.60	1.32	1.07	1.19	1.06	0.75	0.57
β-Globulin	1.03	0.88	1.94	1.63	1.10	0.86	1.04	1.23
γ-Globulin	1.76	1.74	2.01	2.74	2.04	1.53	1.71	2.05
Urinary creatine (mg./8 hr.)	871.5	—	340.1	—	315.0	—	923.8	—
Urinary uric acid (mg./8 hr.)	157.8	—	57.3	—	54.6	—	162.2	—
Urinary amino acid (mg./8 hr.)	7.34	—	2.28	—	1.28	—	7.62	—

testicular tissues from the surviving animals by surgical biopsy under total anesthesia. His findings indicated that the chronically irradiated monkey suffered degenerative processes of the seminiferous tubules of the testes that could be attributed to radiation and appeared to be dose-dependent. His findings also indicated that the regenerative process of spermatogenesis was delayed as a result of irradiation (fig. 5).

At delivery, all animals exhibited symptoms of gastrointestinal disorder, ranging from frequent loose stools to bloody diarrhea (figs. 6 and 7). Fecal examination revealed the following parasites in the majority of animals: *Escherichia coli*, *Bacterium coli*, a "rare *Strongyloides* spp.," an "S. H. D. ova," and *Trichomonas*. The 48 animals were placed on therapy in November 1953, and most were cleared of symptoms by the beginning of the irradiation.

A low incidence of diarrhea recurred during the irradiation interval, being highest in groups G and H, and absent in group E. Virtually no diarrhea was noted in the 90 days after the final exposure, or until February 1956, when all arrivals exhibited symptoms of hypervitaminosis D (11). Following this episode, diarrhea was infrequent, usually occurring a few months before death, and increasing in severity to death. There was some variation among groups in terms of the incidence of diarrhea.

Groups	*Incidence of diarrhea*				
Col. 1	Col. 2	Col. 3	Col. 4	Col. 5	Col. 6
A, B, C, D	15	1	11	2	1
E	6	2	3	—	1
F, G, H	10	7	1	1	1

Col. 2: Number dying after vitamin D episode.

Col. 3: Number having several instances of diarrhea.

Col. 4: Number having diarrhea only at death.

Col. 5: Number not having diarrhea.

Col. 6: Number with single instances of diarrhea other than at death.

TABLE IX

Levels of chemical constituents in the blood of irradiated **Macaca mulatta**

Animal No.	Date	BUN (mg. %)	CO^2 (vol. %)	Na (mEq./liter)	K (mEq./liter)	Ca (mg. %)	P (mg. %)	PO_4
Group A (0 rep)								
33+	5-15-56	23.8	53.8	154	5.2	16.5	4.1	
	6-1-56	25.6	44.8	162	4.2	12.5	4.9	
	6-15-56	24.9	35.8	150	5.4	10.6	4.4	
	1-10-57	20.1		146	4.4		6.9	
34+	5-15-56	26.7	60.4	160	4.3	14.7	5.1	
	6-1-56		58.2	156	4.2	12.5		
	6-15-56	27.1	62.6	150	4.7	11.9	2.9	
	1-10-57	21.7	49.2	142	4.2	11.4	6.0	
Group B (77 rep)								
103+	5-15-56	22.8	53.7	144	4.2	14.1	5.5	
	6-1-56		71.6	162	3.9	11.6	5.1	
	6-15-56	24.9	71.6	138	4.3	11.8	3.6	
Group C (154 rep)								
101+	5-15-56	15.2	62.6	154	4.1	15.5	4.7	9.4
	6-15-56	27.1	58.2	156	5.2	11.8	5.6	
	1-10-57	21.6	52.2	142	6.0	12.4	6.4	
104+	5-15-56	29.5	58.2	148	4.9	13.1	6.0	
	6-1-56	25.9	69.4	153	4.3	11.[illegible]	6.5	
	6-15-56	27.1	62.6	142	4.5	11.6	3.0	
	1-10-57	24.1	80.6	155	4.5	11.2	7.2	
137+	5-15-56	32.8	62.2	204	4.9	15.9	4.5	
	6-1-56	40.5	67.2	150	6.8	14.6	4.7	
	6-15-56	31.5	60.4	146	5.1	12.0	3.3	
	1-10-57	26.3		155	4.7	11.4	6.2	
Group D (308 rep)								
35+	5-15-56	25.2	56.0	152	4.7	13.9	6.2	
	6-1-56		47.2	156	4.8	11.2	5.8	
	6-15-56	25.6	62.6	142	4.8	11.6	3.1	
	1-10-57	24.6	52.2	144	4.8	12.2	5.8	
60+	5-15-56	20.5	53.7	146	4.7	14.7		
	6-1-56	21.4	67.2	120	4.9	11.6	4.4	
	6-15-56	28.2	67.2	146	4.4	12.0	4.4	
	1-10-57	10.6	67.2	149	4.8		5.5	
Group E (0 rep)								
106+	5-15-56	28.2	71.6	204	5.4	13.7	4.5	9.0
	6-1-56		46.0	172	5.8			
	1-9-57	20.5		170	6.3	16.4	10.3	
107+	5-15-56	33.7	58.2	216	4.7	17.5	4.8	8.8
	6-1-56			150	4.2			
	6-15-56	41.4	76.1	142	5.6	14.3	3.0	
	1-9-57	26.8		158	5.0	13.2	6.9	
Group F (156 rep)								
37+	6-1-56		65.3	150	5.4			
	6-15-56	27.1	58.2	146	5.1	11.3	4.8	

TABLE IX (contd.)

Animal No.	Date	BUN (mg. %)	CO^2 (vol. %)	Na (mEq./liter)	K (mEq./liter)	Ca (mg. %)	P (mg. %)	PO_4
56+	5-15-56	24.4	71.6	146	4.5	15.3	5.4	
	6-1-56			156	4.8			
	6-15-56	22.9	62.6	140	4.5	12.0	3.3	
	1-10-57	13.7		148	5.4	12.8	6.4	
135+	5-15-56	31.3	64.9	204	4.7	17.7	5.0	
	6-1-56	29.0	67.2		5.2	14.4	5.5	
	6-15-56	27.9	64.9	140	5.6	12.0	3.9	
	1-29-57	36.1		157	6.3	14.4	6.5	
Group G (308 rep)								
40+	5-15-56	37.3	73.8	148	4.0	15.7	5.5	12.5
	6-1-56			204	5.4			
	6-15-56	30.4	69.4	144	4.5	11.6	4.1	
	1-10-57	22.3	44.8	148	4.4	12.4	7.4	
140+	5-8-56	80.0						
Group H (614 rep)								
52+	5-15-56	33.4	67.2	154	4.6	16.9	5.5	
	6-15-56	25.6	53.7	150	5.9	14.1	4.0	
	1-10-57	16.0		145	5.0	11.3	8.8	

Partial paralysis was noted in 11 animals of the 48 animals, usually of a continuing nature:

Group	*Before death*	*At death*
A	—	1
B	—	1
C	1	—
D	2	—
E	1	—
G	3	—
H	2	—

Alopecia was noted in the records of 20 animals grouped as follows: group A—2; group B—3; group C—1; group D—2; group E—4; group F—2; group G—3; and group H—3.

One animal (294+, group H)—mentioned above in connection with clinical chemistries—differs widely from his group in that he exhibited no abnormal clinical symptoms except a mild case of diarrhea in October 1953 until the vitamin D episode in February 1956. After the vitamin D episode, this animal developed an increasing incidence of diarrhea and anorexia. He became partially paralyzed in 1962 and was sacrificed in January 1964. For approximately 3 months before euthanasia, animal No. 294+ exhibited a microcytic red blood cell population, the MCV being 10 to 15 μ^3 smaller than that of the other survivors.

TABLE X

Findings of ophthalmologic examinations in chronically irradiated Macaca mulatta

Date	Findings
1955	Decreased visual acuity in 614-rep group and suggestion of same in 307-rep group.
Aug. 1956	No lesions seen
Dec. 1956	No lesions seen
Mar. 1957	No lesions seen
Nov. 1957	No lesions seen
June 1958	No lesions seen
Oct. 1959	No lesions seen

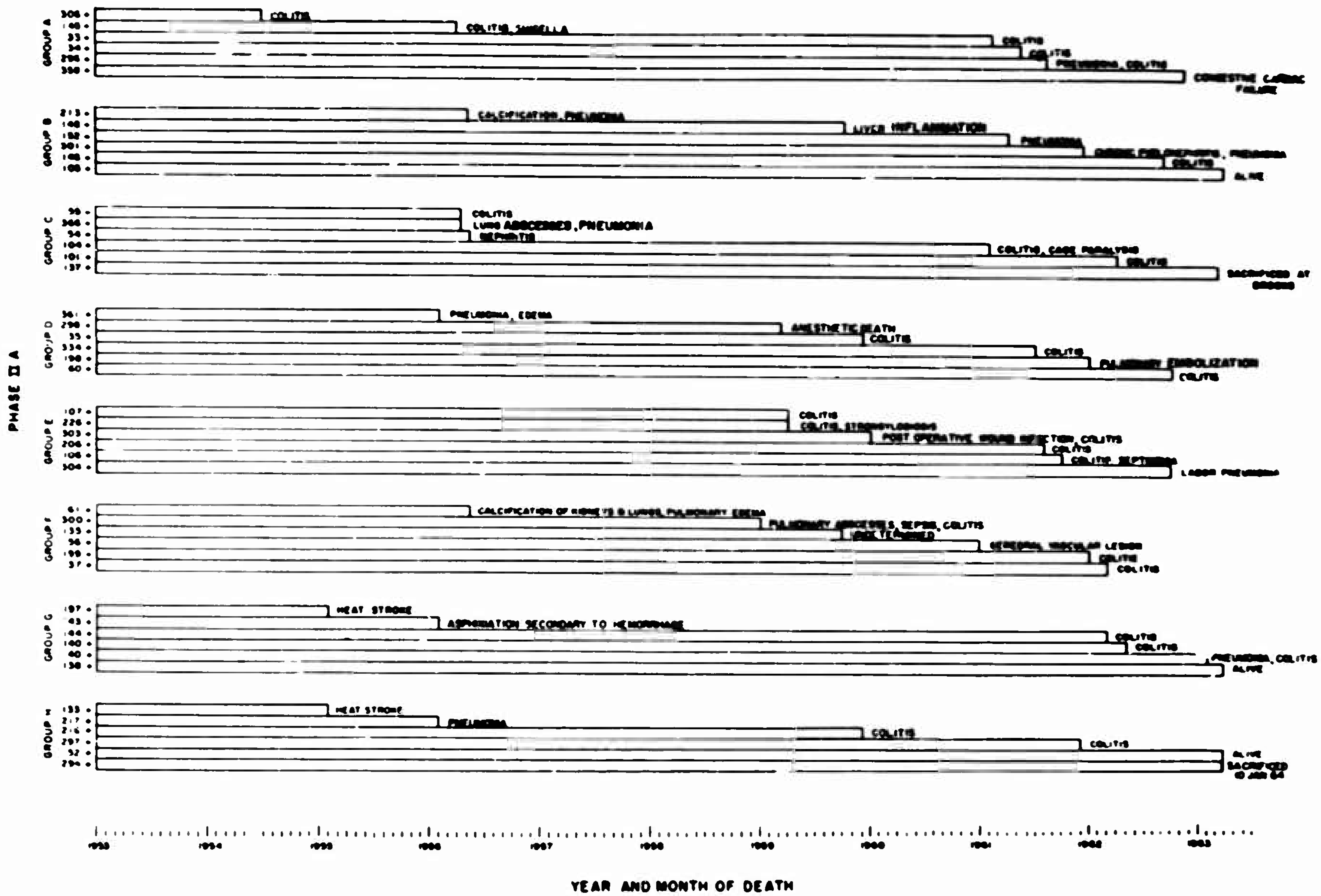

FIGURE 4

Life span of Macaca mulatta *exposed to graded doses of mixed radiation. Autopsy findings associated with death of animal are given.*

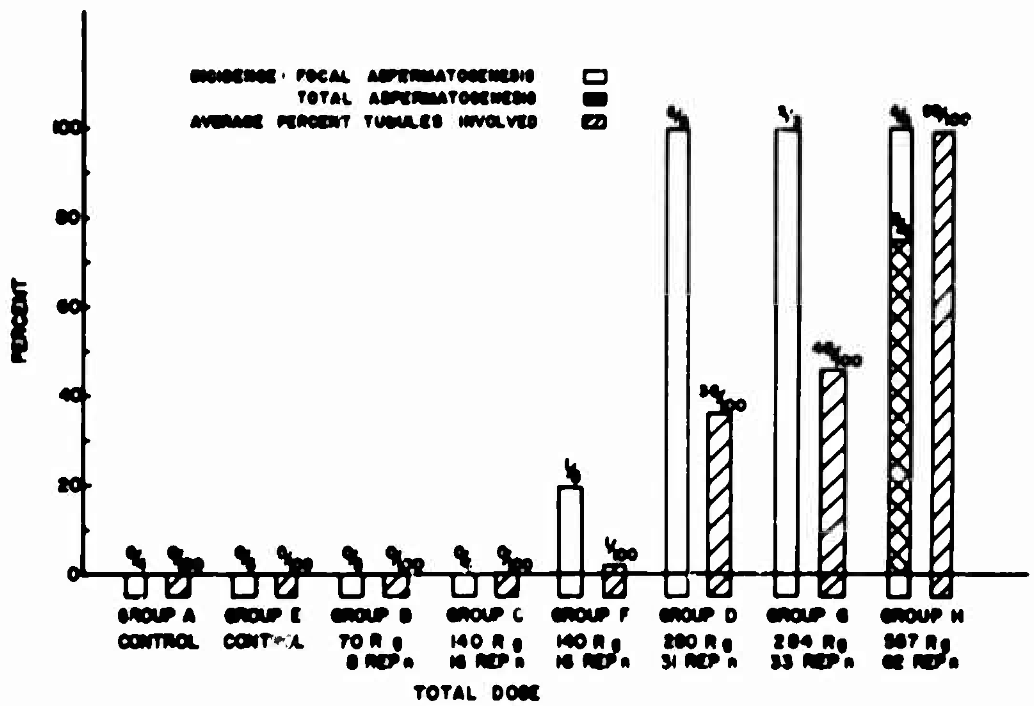

FIGURE 5

Incidence of aspermatogenesis in male Macaca mulatta *exposed chronically to mixtures of gamma rays and neutrons.*

On the day before sacrifice, the hematology included 8.02 million red blood cells, a hematocrit of 49.5%, and a hemoglobin of 14.3 gm. %. Calculations revealed a possible "hypochromic microcytic polycythemia," with MCV= 61.1, MCH = 17.8, and MCHC = 28.9.

The mean body weights for a portion of the experimental period are shown in figures 8 and 9.

Figure 10 offers a direct comparison of the long and short intervals since C and F and D and G are identical in total radiation dose. These values were obtained by averaging 12 weights each year for 3 monkeys which lived the entire period under question. The weights are essentially identical in all groups; where minor differences do appear, the values are not ordered.

Behavioral stu ·es

The single problem tasks on which the monkeys were trained before and during irradiation yielded negative results These tasks included such problems as spatial delayed response, nonspatial delayed response, successive reversal, and an oddity problem (9). Testing on object-quality discrimination learning set, bent-wire detour problems, a finger dexterity test, and linear position preferences during the first 6 months after cessation of exposure also yielded negative results (9).

Suggestion of a radiation-induced change in behavior came from systematic observations of the animals 9 to 10 months after the cessation of exposure (13). At that time the frequency of responses to cage parts as manipulanda, the prepotent stimulus class, was significantly greater for the irradiated monkeys than for the control group. The frequency of responses to uncontrolled auditory stimuli occurring outside the test room (fig. 11) was significantly less for the irradiated than for the control subjects. The greater responsiveness of the irradiated monkeys to the prepotent stimulus class and the depressed responsiveness of the same subjects to outside noises led to a hypothesis of lesser distractibility for the irradiated monkeys than for

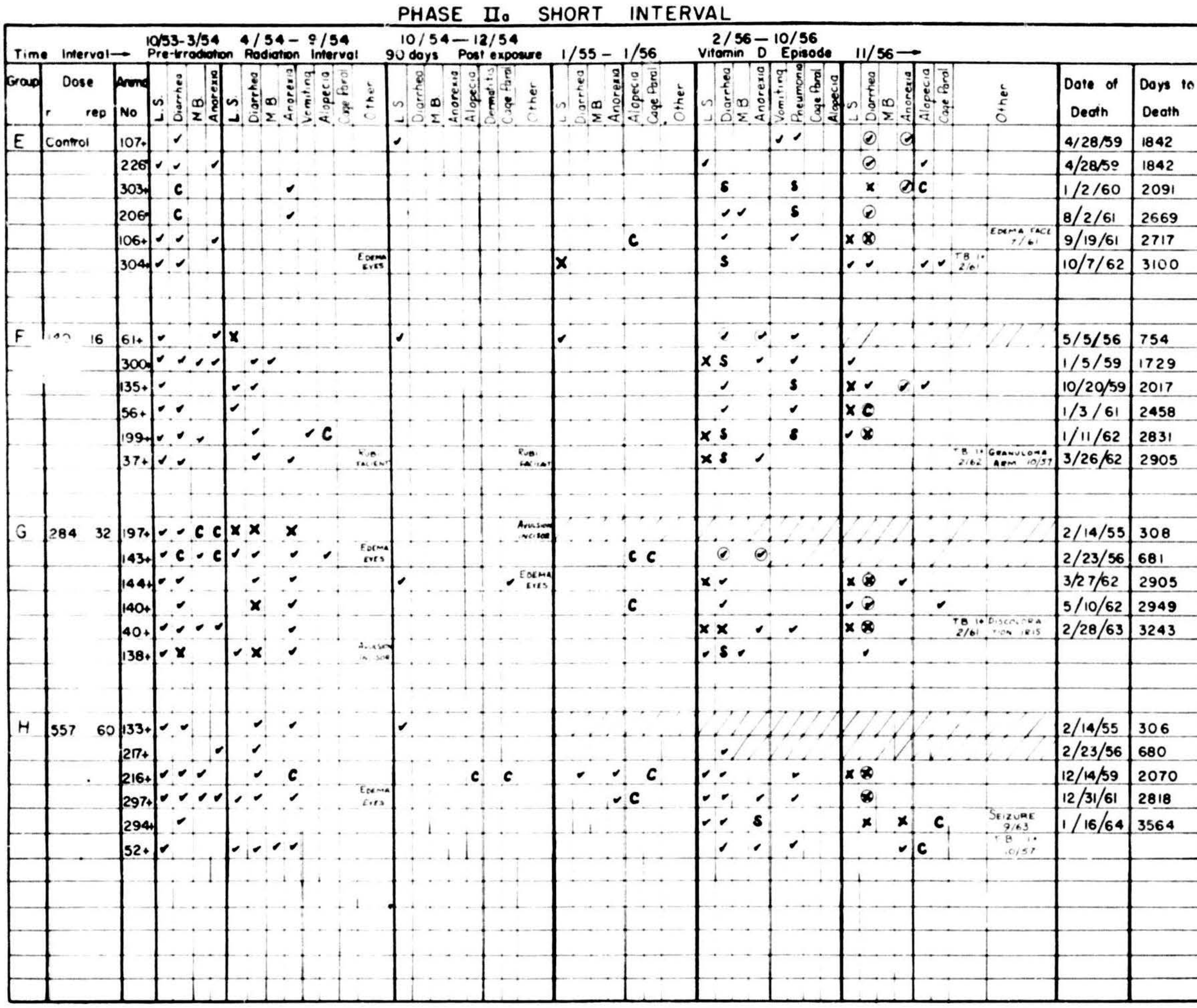

FIGURE 6

Incidence of clinical sequelae in animals exposed every 4 days.

the controls—a hypothesis which was supported by more testing conducted 4 months later (13). These tests showed that *all* experimentally induced stimulus conditions which significantly affected performance latencies of irradiated monkeys on a simple repetitive task also significantly affected the performance latencies of the control animals. The controls, however, were significantly affected by *some* stimulus conditions which did not affect the performance latencies of the irradiated animals.

Davis (8) studied the food preferences of the monkeys 14 to 16 months after exposure, and there appeared to be permanent changes. The experimental animals had a stronger preference for raisins and a greater rejection of celery than had the control group. The irradiated animals also manifested a lower preference for apple and a higher preference for bread than did the control group. These differences, although small, were statistically significant. The changes were interpreted to be, in part, an accentuation of normal

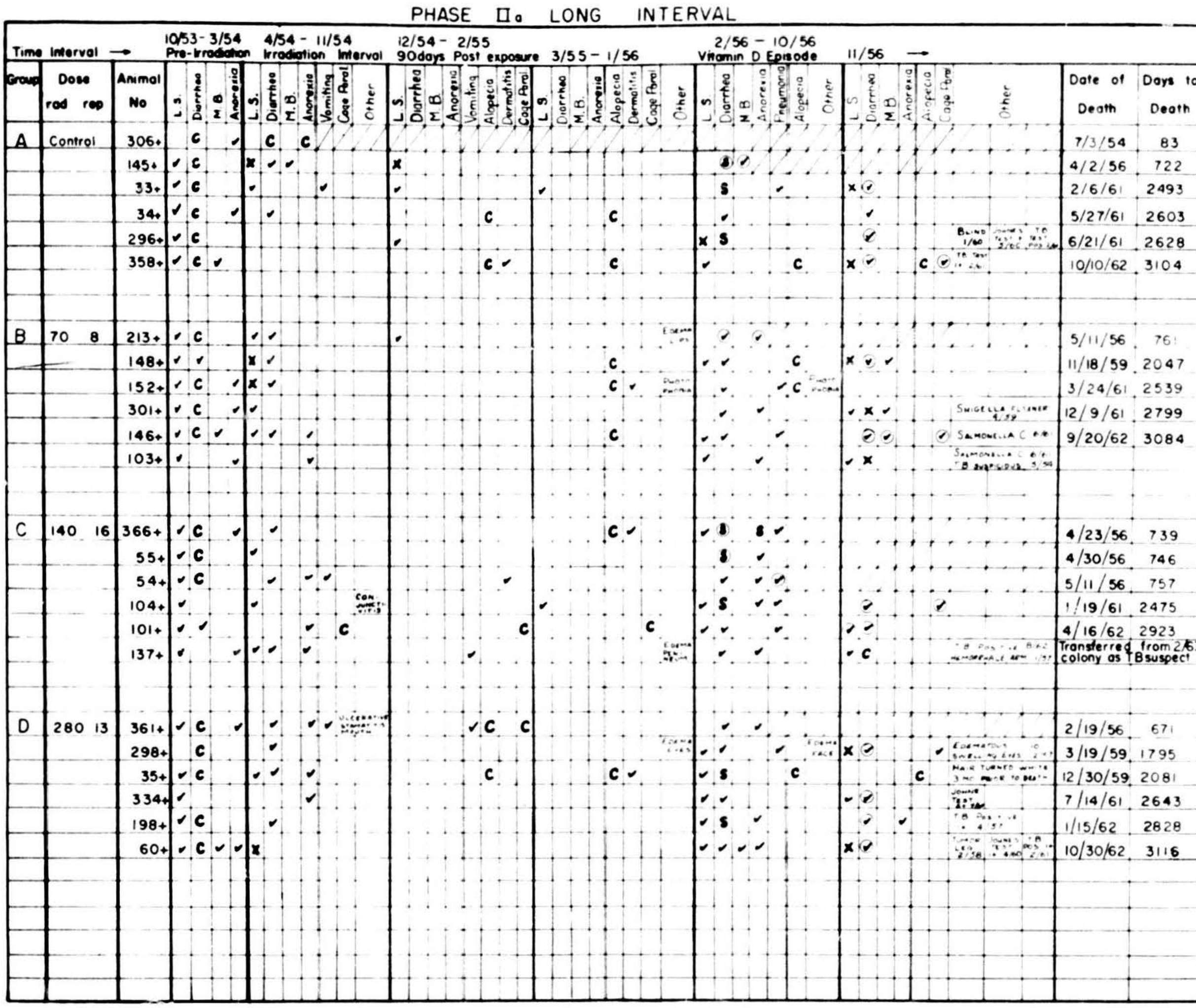

FIGURE 7

Incidence of clinical sequelae in animals exposed every 12 days.

preferences and to be due to radiation damage of the intestinal walls rather than to the caloric value of the food.

The animals were tested by Overall and Brown (26) about 16 months after exposure on a problem to measure scope of attention. The monkeys were given 42 training trials each day on a simple black-white discrimination. Interspersed among each day's training trials were 8 test trials presenting 2 black (positive) stimuli. The control and low-dose irradiated animals, to a significant degree during the test trials, chose the position most recently occupied by the positive training stimulus. The high-dose irradiated animals, however, showed only chance response to that position most recently occupied by the positive training stimulus. The results were considered as indicative of a narrowed scope of attention in the high-dose irradiated monkeys.

Brown et al. (2) hypothesized that a radiation-induced decrease in distractibility with a consequent narrowing of attention should cause the irradiated animals to be less efficient in incidental peripheral cue association than normal subjects. In a test 18 months

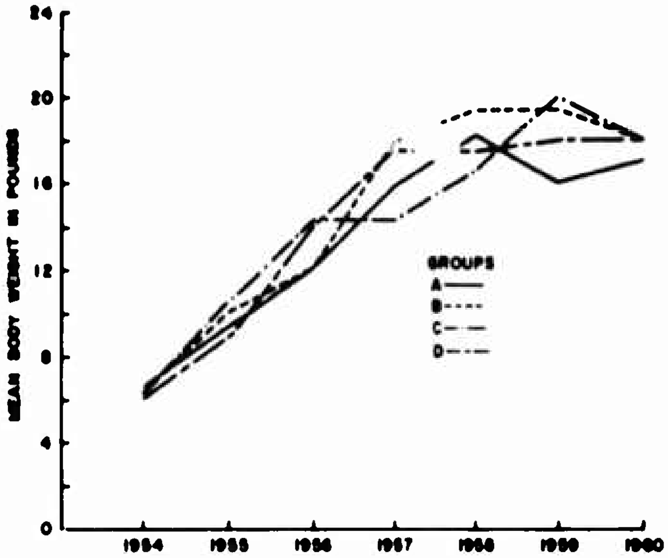

FIGURE 8

Yearly averages of body weight of animals exposed every 4 days.

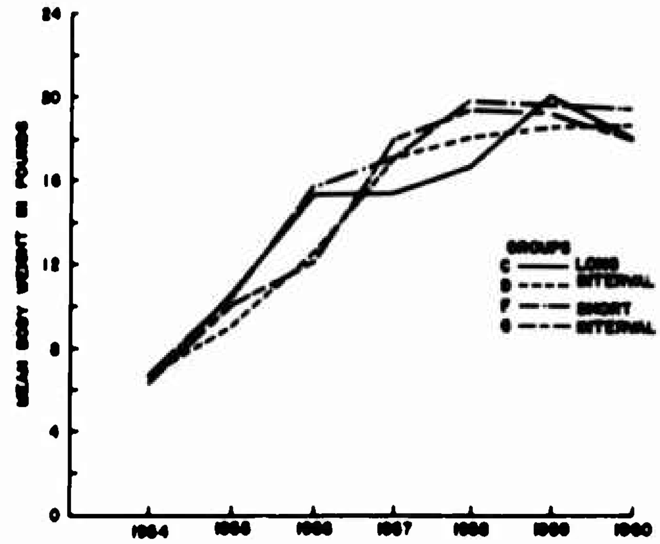

FIGURE 10

Yearly averages of body weight of animals exposed to equivalent radiation doses.

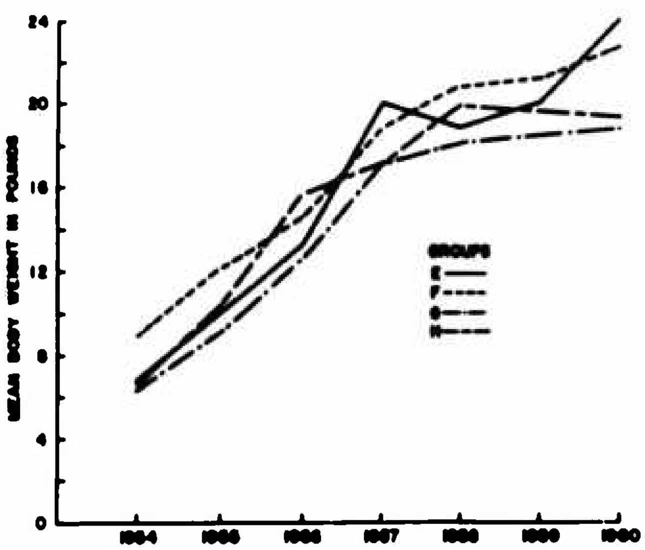

FIGURE 9

Yearly averages of body weight of animals exposed every 12 days.

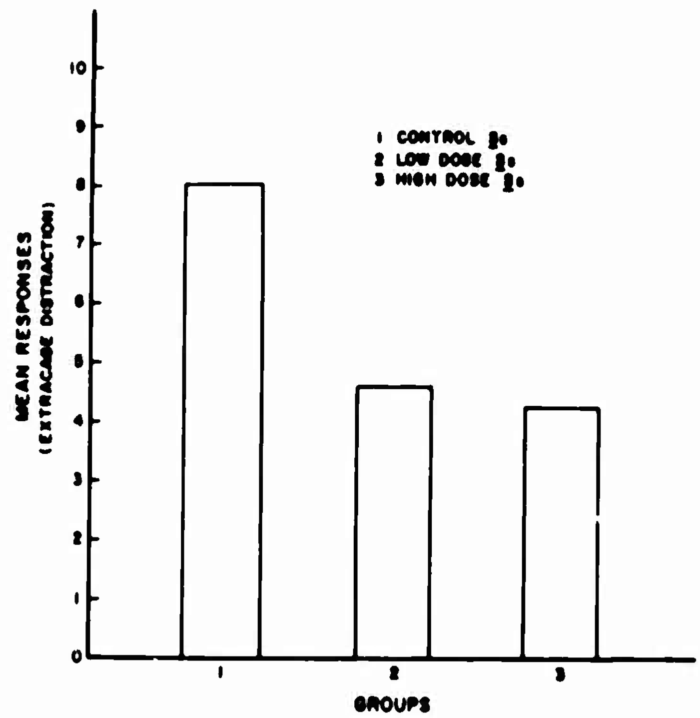

FIGURE 11

Mean responses to extracage distractions by the subjects of each of the three relative radiation dosage groups.

postirradiation, stimuli which were peripheral and incidental on the initial problem became focal on the second problem. The results indicated that the control animals associated the peripheral cues, while the irradiated animals did not.

Overall et al. (28) trained the same monkeys on intermediate-sized discrimination problems. A test of transposition was used to find the degree to which animals in the different subgroups employed relationships between stimuli as a basis for problem solution. Relational learning was found to decrease as a linear function of radiation dosage. The results suggested that the irradiated animals, if

given a choice, will use learning in terms of absolute stimulus properties rather than in terms of relations.

From 18 to 24 months after exposure, the same monkeys were tested by McDowell and Brown (15) on reduced cue discrimination problems. This task combined aspects of object discrimination and delayed response. Two identical cues were placed over the food wells in the Wisconsin General Test Apparatus (WGTA). A discriminable cue was placed on top of that cue covering the food reward during the learning trial of each problem. During the test trial, only the two identical cues were present, and the correct response was to that position rewarded during the training trial. The high-dose irradiated animals showed significantly greater improvement with practice than did the low-dose group or the controls (fig. 12).

Two years after exposure, McDowell and Brown (17) tested the animals on an oddity-reversal problem requiring the use of the same stimulus cues in antagonistic response patterns for correct solution. First, each monkey was tested 24 trials a day to the criterion of 2 successive days with two or less errors per day on response to that object which was odd in color. During reversal, each was tested to the same criterion on response to the object which was odd in form. The groups showed a statistically significant difference in negative savings scores, with the controls having the least savings and the high-dose irradiated monkeys having the greatest savings. The results were interpreted as showing a superiority of the irradiated animals over the controls.

Thirty months after exposure, the monkeys were retested by McDowell and Brown (16) on spatial delayed-response problems. Analysis of the results yielded a significant groups-by-practice interaction. Figure 13 illustrates the effects of differences in distractibility on performance. The controls were initially superior to the irradiated animals, but with continued practice they seemed to suffer interference from stimuli extraneous to the solution of the problem at hand.

Approximately 33 months after exposure, McDowell and Brown (19) compared the response perseveration of some of the same irradiated animals when tested according to a proactive inhibition paradigm. They studied the effects of initial training on a relevant peripheral cue discrimination, during which no learning was manifest, on the subsequent transfer of a single learned discrimination along a peripheral cue gradient. Results indicated that the chronic irradiated male monkey is less susceptible for proactive inhibition than is the normal male monkey.

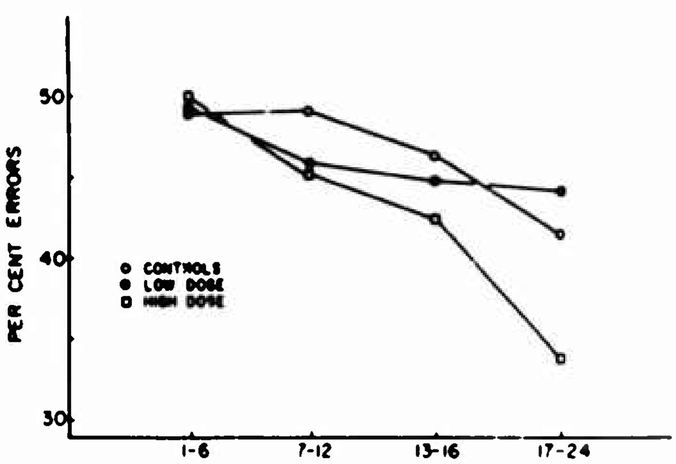

FIGURE 12

Facilitated reduced cue discrimination performance of the high-dose irradiated subjects.

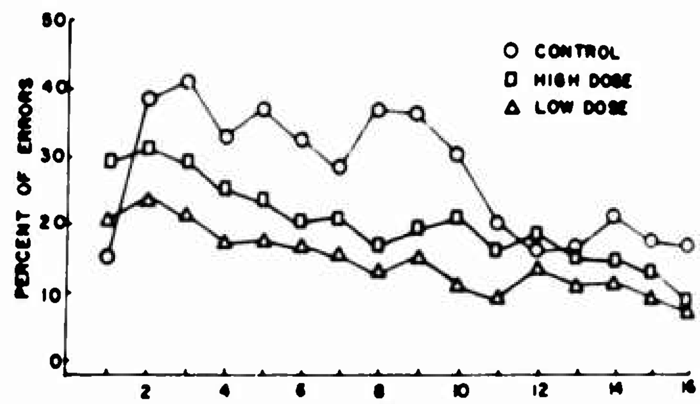

FIGURE 13

Percentage of errors per group per day on the spatial delayed response problem.

During the same period the remainder of the animals were tested by McDowell (14) for the transfer of a single learned discrimination along a peripheral cue gradient. A comparison of the subgroups with respect to transfer efficiency showed them to differ significantly as a nonlinear function of radiation dosage. From the greatest to the least efficiency of transfer, the order is as follows: intermediate-dose group, low-dose group, control group, and high-dose group.

Six months after exposure, Davis et al. (9) had found a suggestion of deficit in visual acuity for the 614-rep group. Brown and McDowell (3) retested the subjects on the same tests about 36 months after exposure. The animals were tested to a criterion of 21 correct responses (24 trials a day) for 2 successive days on each of 8 visual acuity problems presented in order of increasing difficulty. The monkey was required to choose between circles and circles with breaks for a food reward. The high-dose group (614 rep) still showed a visual acuity deficit; in addition, the intermediate-dose group (308 rep) showed a similar deficit.

McDowell and Brown (20) have published work which supports a hypothesis of greater work decrement for normal than for previously irradiated monkeys under conditions of repetitious work. The decrement was manifested as refusal to respond. The proportion of control monkeys showing balks was significantly greater than that for the irradiated animals. The three groups also showed a significant difference with respect to average number of successive days of work without errors or balking (fig. 14). These data indicate that stability over time of increased concentration of attention for whole-body irradiated monkeys is manifest under repetitious work conditions.

A study of the free-cage behavior of these monkeys conducted more than 54 months after exposure shows the continued effect on attention of the irradiation (4). Observations were made of each animal in a free-cage environment with no food for 5 minutes per day for 5 days. The observer recorded on a category sheet the nature and direction of the animal's response

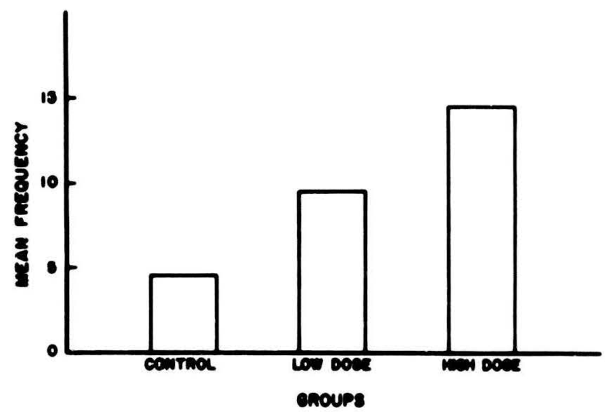

FIGURE 14

Average number of successive days of work without errors or balking for the subjects of each of the three relative radiation dosage groups

every 10 seconds in each observation period. The monkey in this environment could direct his responses to four classes of stimuli including *manipulanda,* the physical features of the cage; *visual* stimuli, the presence of the observer; *self* stimuli, his own body parts; and *auditory* stimuli, randomly occurring noises outside the room. The dependent variable was the relative frequency of each subject's responses to the four stimulus classes. The relative frequency is the total frequency for a specific behavioral response divided by the total frequency of all behavioral responses noted for the animals in the group. When degree of concentration of attention by the monkey is shown exclusively to one stimulus class, maximum variance is achieved. If he responds equally to each of the four stimulus classes, zero variance is achieved. Figure 15 shows the mean variance of stimulus-class responses of 6 controls, 4 monkeys given 154 rep, 4 monkeys given 308 rep, and 4 monkeys given 614 rep. An analysis of this variance data yielded a difference between groups beyond the .05 significance level for a one-tailed test of the theoretic hypothesis. As the radiation dose increased, the mean variance of stimulus-class responses increased. These findings show the increased concentration of attention of the whole-body irradiated animals.

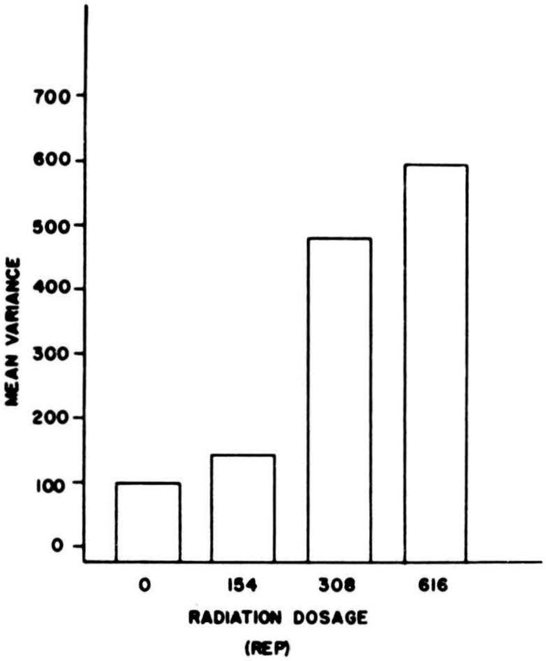

FIGURE 15

Mean variance of stimulus class responses for the subjects of each radiation dosage group.

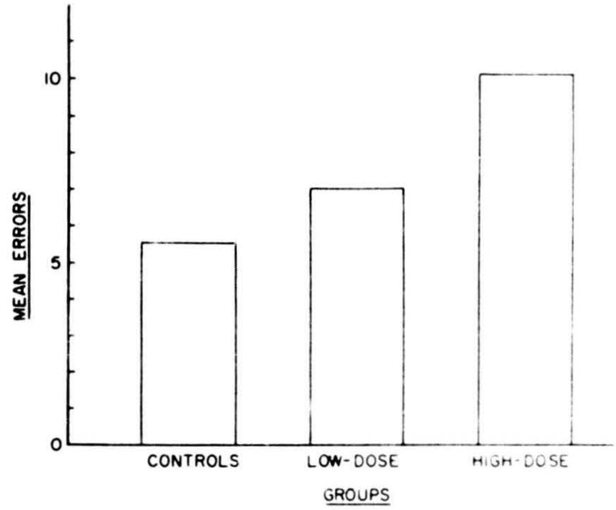

FIGURE 16

Mean errors to initial correct response for the subjects of the three relative radiation dosage groups during 9 days of successive reversal training.

Some 78 months after exposure, the monkeys were tested for 10 days by McDowell and Brown (23) on between-day reversal learning. A two-object discrimination problem was used with the valences of the objects held constant within each day of testing, but alternated between successive days of testing. The groups (fig. 16) differed with respect to errors to initial correct response on the 9 days of reversal testing. This difference was beyond the .005 significance level. The difference probably reflects an increased capacity for retention between days of training for the irradiated animals.

Over 7 years after exposure the surviving primates were tested for stability of behavior under conditions of social distraction (21). Each animal was observed under a condition of no social distraction, with a female monkey at menses present, and with a female monkey at estimated time for ovulation present. Order of condition presentation was balanced over days within each radiation subgroup. The female was visually, but not physically, accessible; the holding cage was placed 3 feet from the cage housing the experimental animal. One month later the study was replicated. In both studies, stability of behavior was disrupted by social distractions except in the high-dose (614 rep) group.

The last test was conducted about 90 months after exposure (22). Since numbers were now small, the only comparisons made were between the controls as one group and the irradiated monkeys, irrespective of dose, as the second group. Each animal was tested for 24 trials on a single discrimination problem and, then, was immediately tested for 24 trials with neither stimulus rewarded. Response latency was recorded on each trial. With an extinction criterion of failure to respond within 50 milliminutes, it was found that the irradiated monkeys extinguished significantly faster than did the controls.

The monkeys were tested on several theoretic problems in which radiation failed to be a significant factor: conceptual discrimination (7), novelty learning set (6), response to probabilistic sequential dependencies (27), transpositional responses to stimulus objects of intermediate size (10), response shift learning set (5), and peripheral cue learning set (18).

V. DISCUSSION

The objective of this research was to describe the effects of ionizing radiation upon a species of primate when that animal received

the irradiation in frequently spaced portions over a relatively long period of time. While the data obtained from studies on *Macaca mulatta* are, at best, suggestive of the effects of chronic irradiation on USAF personnel in aerospace vehicles, the information can be used to anticipate the nature and severity of any effects.

It is interesting that the experimental design of this phase profited from the rather innocuous results seen in the Reactor irradiations (25). In terms of total dose alone—assuming an RBE for fast neutrons of 10—the highest rem dose in the first phase was 512. This design was first to reach only 320 rem. The design which was executed (table II) achieved 1,120 rem in the highest dose group. The results demonstrate that even this dose cannot be considered highly damaging even when there are just 4 days to recoup. As a result of the new data, two further studies were designed in the series; both of these separated the neutron and gamma ray doses, and the second of the two carried the total doses upward by factors of 2 to 10.

There have been variations in the neutron doses reported as received by the animals. In the original design, the total doses and dose rates were determined on the basis of a first collision conversion factor of 4.0×10^{-9} rep/neutron/cm.^{2} It was later stated by Hurst and Auxier (35) that for a nonenergy-degraded PoBe neutron, the factor should very probably be 4.65×10^{-9} rep/neutron/cm.^{2} Such a change in factors results in a calculated neutron dose, which is some 6% higher than originally reported. Additional calibration work by Sigoloff, using the USAF chemical dosimeter, indicated that for the environment of the Mixed Irradiation Facility, there was degradation of neutron energy and that 4.0×10^{-9} rep/neutron/cm.^{2} was the better figure for calculations of the neutron dose. It must be emphasized that the variations lie in the choice of a conversion factor rather than in any ambiguity in the measured neutron flux. Table XI will enable the reader to convert to other radiation dose units now in use.

The course of the research was not smooth. Data concerning the life span of the animals were compromised by the hypervitaminosis D incident; 5 deaths were attributed directly to the effects of large doses of dietary vitamin D. The part that this vitamin intoxication played in enhancing death from the other causes noted can only be speculated upon. The lethal effects of the irradiation on either schedule were also

TABLE XI

Flux-to-dose conversion factors

Neutron energy (Mev)	Multiple collision calculation at dose—		First collision calculation at neutron dose—	
	rep/n/cm.^{2}	rad/n/cm.^{2}	rem/n/cm.^{2} using fixed RBE	rem/n/cm.^{2} NBS Handbook '59 values of RBE
10	6.04×10^{-9}	5.62×10^{-9}	6.45×10^{-8}	3.50×10^{-8}
5	4.81×10^{-9}	4.48×10^{-9}	4.90×10^{-8}	2.90×10^{-8}
4	4.61×10^{-9}	4.29×10^{-9}	4.76×10^{-8}	3.00×10^{-8}
3	3.96×10^{-9}	3.68×10^{-9}	3.94×10^{-8}	2.65×10^{-8}
2	3.33×10^{-9}	3.10×10^{-9}	3.32×10^{-8}	2.50×10^{-8}
1	2.66×10^{-9}	2.47×10^{-9}	2.47×10^{-8}	2.60×10^{-8}

Adapted from table 14-1, "Flux at neutrons corresponding to 1 rad or 1 rem." Morgan, K. Z. Determination of exposures. *In* Blatz, H. (ed.). Radiation hygiene handbook, 1st ed. New York: McGraw-Hill Book Co., 1959.

clouded by the relatively high mortality rates that prevailed in the colony: deaths were attributed to colitis, pneumonia, nephritis, and accident. This experiment involves a period of 10 years, in which 45 of the 48 animals expired: 43 animals died within 9 years; 2 animals died during the 10th year; 3 animals are still alive. The life expectancy of the macaque is not well known—estimates range from 15 years in captivity to 30 years—but it is evident that the animals in this study have not lived as long as others under different circumstances. It is our feeling that the radiation factor in the present circumstances cannot be implicated as a primary cause of life-shortening or mortality. It is extremely difficult, however, to extricate the intrinsic factors of the experimental design from the many other factors which have been brought to bear on these monkeys.

Decreases in peripheral blood cell levels have resulted from the fact of irradiation. The white blood cell effects are not unexpected; the red blood cell effect was somewhat more unique. A significant erythrocyte depression occurs only in the short-interval group, and then only in the high-dose (614 rep) group. It is probably not of great clinical importance. All the effects are also undoubtedly transient at the dose levels in this experiment.

It will be seen at once that groups C, D, F, and G offer a possible comparison for a given parameter of the effect of the 4-day and 12-day interval schedules on any perceivable damage. This comparison was made for mean yearly weights in figure 10, but no effect was noticeable, perhaps because of the grossness of the measure. In figure 3, however, the comparisons can be made for a more sensitive effect. The hematologic data suggest that the depressions in white blood cell counts are proportional only to total dose and that 308 rep of these mixed radiations are very probably enough to achieve the depressions noted. In the red blood cell counts the decreases are in order of both schedule and total dose. The order is as one would predict; i.e., the shorter schedule (4-day interval) is the more damaging. The 614-rep group also seems to suffer a greater depression than the 308-rep group when the starting points are aligned.

Pitcock's data (30) show that irradiation also causes testicular damage in the form of evidence of histologic sterility and that such damage is dose-dependent. It must be remembered, however, that the animals were not fully mature when the irradiation was commenced. There is also evidence of pathologically demonstrable incidence of a demyelinating disease which increases as a function of chronic irradiation.

Ophthalmologic examinations and performance trials reveal that these fractionated irradiation sequences did not cause radiation cataracts in the monkey, but that there was a decrement in visual acuity. This loss of visual ability was not associated with anatomic lesions and was observed only in animals exposed to 308 and 614 rep.

The behavior and performance testing suggests that personnel receiving successive small doses of radiation could very possibly experience a loss of performance efficiency on tasks requiring concurrent response to several stimuli; on the other hand, facilitated performance might be expected in situations involving minimal stimuli which are in the proximity of the focus of attention. Indeed, the general behavioral results could possibly be extrapolated to the human were it not for the fact that the emotional trauma consequent upon the knowledge of exposure in the human would probably nullify the effects. The greatest value of the behavioral findings lies not in their specific nature, but in their demonstration that whole-body exposure to sublethal doses of radiation produces effects which persist for at least several years after the fact of exposure and probably for the lifetime of the exposed organism.

Many clinical findings have been remarked in the course of this report; none of these would appear to be primary effects of the radiations as administered. There is little doubt, however, that certain of the clinical observations should be examined closely without restricting oneself to radiation-induced effects. Despite the value which such results would have, the authors felt that such an evaluation was outside the purview of this report.

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13. ABSTRACT

The radiobiologist has been concerned with both the early and late effects of ionizing radiations administered in small increments over a relatively long period of time. In 1954, 48 Macaca mulatta primates were exposed to an irradiation schedule involving fast neutrons and gamma rays which resulted in the accumulation of doses from 77 to 614 rep. Since the exposure schedules afforded rest and recovery periods, it was proposed and found that the effects were less severe than the effects from comparable doses given acutely.

The principal early effect noted was a transient decrease in peripheral cell counts for leukocytes and erythrocytes noted in the higher dose group. The principal late effects involved a reduction in visual acuity in the 307- and 614-rep groups; a series of definitive, continuing behavioral changes; and evidence of dose-dependent testicular damage as noted by histopathologic methods. Evaluation of the data suggests that radiation was probably not a factor in life-shortening.

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